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Chemotherapy Dose Intensity and Survival in Non-small Cell Lung Cancer

To the Editor:

Brunetto et al.[1] noted that modest chemotherapy dose reductions did not have any major impact on survival in patients with non-small cell lung cancer (NSCLC) treated with platinum-doublet chemotherapy and proposed that this might be due to comorbidities, the impact of resistance factors such as excision repair cross-complementing rodent repair deficiency, complementation group 1 (ERCC1) or marked sensitivity to therapy in some of the responders. We had previously converted response rates into hypothetical mean percent tumor cell kill for a large number of published clinical trials in NSCLC and had used nonlinear regression analysis to assess the relationship between hypothetical log mean cell kill and planned dose intensity.[2] For all platinum combinations assessed, dose-response curves flattened at higher chemotherapy doses. Low chemotherapy doses were better than no therapy, but high doses were no better than low doses.

We had previously hypothesized that one could infer resistance mechanisms from the shape of the dose-response curve and that presence of a resistance factor (e.g., the ERCC1 mentioned by Brunetto et al.) would give a shoulder on the dose-response curve when log cell survival was plotted against linear doses (analogous to competitive inhibition of drug effect).[3] Mutation of an obligate target or activating system, would give a reduced slope on the curve, analogous to decreased affinity of a drug for its target.[3] Deficiency or saturation of something required for drug effect (e.g., a drug uptake or activating system, proapoptotic factors, or cells in a sensitive phase of the cell cycle) would give an initial downward slope followed by a terminal plateau (analogous to noncompetitive inhibition of drug effect).[3]

On the basis of our hypothesis and on our observation of the flattening of the dose-response curve in NSCLC, we postulated that our inability to cure metastatic NSCLC with chemotherapy is ultimately due to deficiency or saturation of something required for drug efficacy. Furthermore, as no metastatic epithelial cancer can be cured even by high-dose chemotherapy, we hypothesized that all epithelial cancers (e.g., breast, colorectal, and lung cancers) may share a common reason for this incurability.[2] For different epithelial cancers or for different patients with the same type of cancer, a higher or lower maximum cell kill may be achievable, and it may take fewer or more drugs or higher or lower doses to achieve this maximum cell kill, but the outcome is ultimately the same. Resistance factors such as ERCC1 could affect degree of palliation in individual patients but would not in themselves be responsible for incurability.

A corollary of this is that, even if all epithelial cancers are incurable when metastatic, higher drug doses, or addition of more agents may be useful for relatively sensitive tumors such as breast and small cell lung cancer (SCLC) but would be much less useful for more resistant tumors such as NSCLC and pancreatic cancer. In keeping with this, when we did the same type of analysis in SCLC as in NSCLC, the maximum achievable cell kill was greater in SCLC, and cell kill seemed to keep increasing over a wider dose range, but a maximum possible cell kill was nevertheless ultimately reached.[4]

A second corollary is that if we are correct that a common mechanism is responsible for the incurability of all epithelial malignancies, then a single new approach targeting this mechanism could similarly have a dramatic impact on outcome of a broad spectrum of epithelial malignancies.

David J. Stewart, MD, FRCPC
Department of Thoracic/Head and Neck Medical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

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Clinical Significance of Serum Vascular Endothelial Growth Factor in Malignant Pleural Mesothelioma

To the Editor:

We read with great interest the article by Yasumitsu et al.,[1] who reported the clinical significance of serum vascular endothelial growth factor (VEGF) in malignant pleural mesothelioma (MPM). VEGF is an important regulator of angiogenesis and might have critical roles in MPM progression. Demirag et al.[2] demonstrated a significant correlation between

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Address for correspondence: David J. Stewart, MD, FRCPC, Department of Thoracic/Head and Neck Medical Oncology, M. D. Anderson Cancer Center, Houston, TX 77030. E-mail: dstewart@mdanderson.org

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Address for correspondence: Nobukazu Fujimoto, MD, PhD, Department of Respiratory Medicine, Okayama Rosai Hospital, 1-10-25 Chikkomidorimachi, Minamiku, Okayama 7028055, Japan. E-mail: nfuji@okayamaH.rofuku.go.jp

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